

allowing for the rejoinder of claims 21, 22, 25-28, and 35-40. Finally, Applicants submit that the entry of the Amendment would place the application in better form for appeal, should the Office dispute the patentability of the pending claims.

**Request for Rejoinder of Claims 21, 22, 25-28, and 35-40
upon Allowance of Claims 11-13, 16-18, and 29-34**

Applicants respectfully request that non-elected process claims 21, 22, 25-28, and 35-40 be rejoined to claims 11-13, 16-18, and 29-34 in accordance with 37 C.F.R. § 1.141 and M.P.E.P. § 821.04. (Claims 21, 22, 25-28, and 35-40 correspond to claims 21-28 pending at the time of the March 27, 2002, restriction requirement.)

Section 821.04 of the M.P.E.P. states that if an applicant elects to prosecute a claim to a product, as here, withdrawn process claims that "depend from or otherwise include all the limitations of the allowable product claim will be rejoined." Applicants note that claims 21, 22, 25-28, and 35-40 depend directly or indirectly from claim 11 or claim 12, and therefore, contain all of the elements and limitations of these claims. Thus, claims 21, 22, 25-28, and 35-40 are rejoinable process claims according to 37 C.F.R. § 1.141 and M.P.E.P. § 821.04.

Rejection under 35 U.S.C. § 112, first paragraph

The Office rejected claims 11-13, 16-18, and 29-34, as allegedly lacking written description support. The Office contended that "an immobilized enzyme comprising material derived from more than one source" is not supported in the specification. This rejection is moot upon entry of the proposed amendments to claims 11 and 16.

Therefore, Applicants request the entry of these amendments and the withdrawal of this rejection.

In any event, Applicants note that while the literal language of claims 11 and 16 recites "an immobilized enzyme," one of ordinary skill in the art would understand that these claims cover carriers on which more than one enzyme molecule is immobilized. Because the specification discloses (S)-hydroxynitrile lyase enzymes derived from *Euporbiaceae*, *Poaceae* (*Gramineae*), and *Olacaceae* sources, Applicants submit that one of skill in the art would recognize that a single carrier according to claims 11-13, 16-18, and 29-34 can have (S)-hydroxynitrile lyase enzymes from a single source, or from more than one of these sources immobilized on it. Thus, Applicants submit that the specification provides support for these claims and that the amendment to claims 11 and 16 does not change the scope of the claimed invention.

Rejection under 35 U.S.C. § 112, second paragraph

The Office rejected claims 11-13, 16-18, and 29-34 as allegedly indefinite. Specifically, the Office objected to the term "absorbed" in claims 11, 16, 31, and 34, contending that it is confusing and should be changed to "adsorbed." Applicants have amended the claims solely to advance prosecution, rendering this rejection moot.

Nevertheless, Applicants submit that "absorb" and "adsorb" are both routinely used to describe the immobilization of a protein on a solid matrix, and that both terms encompass immobilization on the surface of a matrix as well as inside the accessible pores of that matrix. Thus, Applicants submit, that "absorb" is definite, and that this change of wording does not alter the scope of the claimed invention.

The Office also objected to the recitation of "*Poaceae* (*Gramineae*)" in claims 11 and 16 because *Poaceae* and *Gramineae* refer to the same taxonomic family, and suggested that only one of the names be used. Applicants note that the meaning of

"*Poaceae (Gramineae)*" is clear, and that this term is used interchangeably with the terms "*Poaceae*" and "*Gramineae*" when referring to this family of grasses. (See page 6 and Exhibits A and B of Applicants' remarks filed August 23, 2002.) However, Applicants have amended claims 11 and 16 solely to advance prosecution. Because "*Poaceae*" and "*Poaceae (Gramineae)*" have the same meaning, this change of wording does not change the scope of the claimed invention.

While these rejections are moot in light of the present amendments, Applicants submit that they are entitled to be their own lexicographers. M.P.E.P. § 2111.01. Moreover, only a reasonable level of particularity and distinctness is required to comply with 35 U.S.C. § 112. M.P.E.P. § 2173.02; emphasis in original. The M.P.E.P. also points out that the Office "should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement." *Id.*

Finally, the Office rejected claims 11 and 16, contending that the recitation of "one or more of" is indefinite. As stated above, those claims have been amended to remove this phrase. Thus, this rejection is now moot.

Nevertheless, as explained above, one of ordinary skill in the art would recognize that these claims cover carriers on which more than one enzyme is immobilized. Thus, the immobilized enzymes on a carrier may be derived from more than one claimed source. Thus, Applicants submit that claims 11 and 16 are definite.

Rejection under 35 U.S.C. § 103(a)

The Office maintained the rejection of claims 11-13, 16-18, and 29-34 as allegedly obvious over the combination of the three "Wehtje" articles (*Appl. Microbiol. Biotechnol.*, 29: 419-25 (1988); *Biotechnol. Eng.*, 36: 39-46 (1990); and *Biotechnol.*

Eng., 41: 171-8 (1993)), Effenburger et al. (U.S. Patent No. 5,885,809) and Andruski et al. (U.S. Patent No. 5,177,242). (Applicants note that recitation of "Altshuler" in place of "Andruski" at pages 11-12 of the previous response was the result of a typographical error.)

Applicants appreciate that the Office recognized that the immobilized enzymes disclosed by Wehtje are not the same as the enzymes claimed herein and withdrew the rejections under Section 102. However, in maintaining the present rejection under Section 103, the Office has not considered the impact of this difference in enzymes. Indeed, as set forth below, this difference undermines completely any expectation of success of obtaining the claimed invention. In addition, in maintaining this rejection, the Office has relied upon a combination of Wehte with the teachings of Effenburger and Andruski without identifying any motivation in the art to make this combination. Thus, the maintained rejection is not based on a *prima facie* case of obviousness. Without a showing of any motivation for one of ordinary skill in the art to combine the teachings of Effenburger and Andruski with those of the Wehtje articles and/or without any reasonable expectation of success in doing so, the Office has not set forth a *prima facie* case of obviousness. M.P.E.P. § 2143.01.

Indeed, far from suggesting any desirability of combining these references, both Effenburger and Andruski would teach that no change is needed. Effenburger describes the use of nitrocellulose carriers as "resulting in a distinct increase both of the yield of (s)-cyanohydrines as well as of the enantiomeric excess, a result which is not readily foreseeable compared with a traditional cellulose carrier material." (See col. 3, lines 40-45.) Thus, Effenburger teaches that nitrocellulose is a worthy improvement.

This express satisfaction with nitrocellulose as a carrier simply cannot motivate a skilled person to try any other carrier, let alone the claimed porous inorganic material which have different properties from the carriers claimed herein.

The same defect lies in Andruski which employs an intermediate crosslinking agent, such as PEI, through which the enzyme is covalently attached to the carrier. The article by Messing, submitted with the attached form 1449, explains how crosslinking differs from "adsorption" immobilization methods. (See Messing at page 149, first and second full paragraphs.) Andruski points out that, when one wishes to obtain an optically active cyanohydrin from an (S)-hydroxynitrile lyase, crosslinking with polyethyleneimine (PEI) allows for faster reaction times and easier handling of reagents than various prior art methods, including Effenburger's method. (See Andruski at col. 2, lines 5-15; col. 1 at lines 15-46.) Andruski also points out that chemical cross-linking is advantageous because "the enzyme remains affixed to the membrane for several days at a time," and because cross-linking "represents a more stable and durable arrangement compared to prior art methods." (*Id.* at col. 3, lines 62-68.) Again, the clear satisfaction with this system cannot provide any motivation for using another system. Accordingly, the Office has not set forth any motivation to combine the references.

Moreover, there is no reasonable expectation of success in the combination. As noted above, the Office has correctly noted that none of the three Wehtje articles refer to the claimed S-hydroxynitrile lyase proteins. However, the Office has not appreciated that the difference between the Wehtje (R)-hydroxynitrile lyase and the claimed (S)-hydroxynitrile lyase completely undermines any reasonable expectation of success.

The three Wehtje articles refer to immobilization of the (R)-hydroxynitrile lyase from almond, which, despite its similar-sounding name and similar biological function, is an unrelated protein with a completely different structure and catalytic mechanism from the claimed (S)-hydroxynitrile lyase proteins. For example, Exhibit A shows that (R)-hydroxynitrile lyase has only 15.68% sequence homology with a representative, claimed (S)-hydroxynitrile lyase protein, indicating that they are not related. Indeed, those of skill in the art have concluded from a variety of evidence that these two classes of proteins are not structurally related and evolved independently, as the publications submitted herewith in the PTO form 1449 illustrate. (See also Wajant et al., *Plant Science* 108: 1-11 (1995), Hughes et al., *Arch. Biochem. Biophys.* 311(2): 496-502 (1994), and Seely et al., *J. Biol. Chem.* 241(19): 4457-4462 (1966), previously submitted.) Because these articles are provided as evidence to rebut the Office's contentions, their submission in the attached PTO form 1449 need not comply with the requirements of 37 C.F.R. §§ 1.97 and 1.98 for them to be considered by the Examiner. See M.P.E.P. § 609 at page 600-132.

In consequence of these teachings, one of ordinary skill in the art cannot reasonably predict from Wehtje's teachings of (R)-hydroxynitrile lyases whether the claimed (S)-hydroxynitrile lyase proteins could be successfully adsorbed onto the claimed inorganic carrier materials because whether a protein will adsorb onto the carriers and retain its catalytic activity depends on the structural characteristics of the protein, such as its surface electrostatics and its shape. Indeed, the 1993 article by Wehtje states that:

Adsorption of proteins onto surfaces [is] known to involve some degree of conformational changes in the protein molecule. Hydrophobic interactions within the protein structure are important for the overall stability of the protein molecule. Upon adsorption these hydrophobic interactions may be disturbed and hydrophobic parts may instead interact with the support, with a subsequent change in the protein structure.

(Wehtje 1993 at page 177, col. 1, last full paragraph, citations omitted.) The article goes on to state that such changes, resulting in enzyme deactivation, have been observed. (*Id.*) In addition, Messing teaches that active site structure is an important factor to consider in whether a protein will be successfully adsorbed to a carrier and retain activity. (Messing at page 153, first and second full paragraphs.) (R)- and (S)-hydroxynitrile lyases have completely different catalytic mechanisms, and thus completely different active site structures. Accordingly, there is no reasonable expectation that the claimed immobilized (S)-hydroxynitrile lyases could be obtained successfully.

Because there is no motivation for one of ordinary skill in the art to combine the teachings of Wehtje, Effenburger, and Andruski, as well as no expectation of success in doing so, claims 11-13, 16-18, and 29-34 are not obvious over these publications. Thus, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is in condition for allowance. Applicants therefore request the reconsideration and reexamination of the application, the timely allowance of claims 11-13, 16-18, and 29-34, and the rejoinder of claims 21, 22, 25-28, and 35-40.

Please grant any extensions of time required to enter this response and charge any required fees not submitted herewith to our Deposit Account No. 06-0916.

Respectfully submitted,

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APPENDIX TO THE AMENDMENT OF JANUARY 22, 2003

Version Showing Changes Marked-Up

Amendments to the Claims:

11. (Twice Amended) An immobilized enzyme comprising (S)-hydroxynitrile lyase derived from [one or more of] *Euphorbiaceae*, *Poaceae*, [(*Gramineae*), and] or *Olacaceae* [absorbed] adsorbed on a carrier comprising a porous inorganic material.

16. (Twice Amended) A method for producing an immobilized enzyme, comprising [absorbing] adsorbing (S)-hydroxynitrile lyase derived from [one or more of] *Euphorbiaceae*, *Poaceae*, [(*Gramineae*), and] or *Olacaceae* on a carrier comprising a porous inorganic material.

31. (Amended) The immobilized enzyme according to claim 11 or 12, wherein the pH at the time of enzyme [absorption] adsorption is between 4.83 and 6.79.

34. (Amended) The method for producing an immobilized enzyme according to claim 16 or 17, wherein the pH at the time of enzyme [absorption] adsorption is between 4.83 and 6.79.

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